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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: TRANSDERMAL THERAPEUTIC SYSTEMS COMPRISING PHOTOSENSITIVE ACTIVE SUBSTANCES

(54) Bezeichnung: TRANSDERMALE THERAPEUTISCHE SYSTEME MIT LICHTEMPFINDLICHEN WIRKSTOFFEN

(57) Abstract: The invention relates to transdermal therapeutic systems (TTS) whose structure consists of a polymer matrix, which contains active substances, and of a backing layer. The inventive systems comprise a content of at least one photosensitive active substance and are characterized in that said TTS contain at least one colorless substance. The colorless substance absorbs light in the UV region, does not have any inherent pharmacological action, is dispersed or dissolved in the polymer matrix of the TTS, and/or is homogeneously distributed in the backing layer of the TTS.

(57) Zusammenfassung: Transdermale therapeutische Systeme (TTS), deren Aufbau eine wirkstoffhaltige Polymermatrix und eine Rückschicht umfaßt, mit einem Gehalt an mindestens einem lichtempfindlichen Wirkstoff, sind dadurch gekennzeichnet, daß die genannten TTS mindestens eine im UV-Bereich absorbierende, farblose Substanz enthalten, die keine eigene pharmakologische Wirkung aufweist, und die in der Polymermatrix des TTS dispergiert oder gelöst ist und. und/oder die in der Rückschicht des TTS homogen verteilt ist.

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Transdermal therapeutic systems with photosensitive active ingredients.

The present invention concerns transdermal therapeutic systems (TTS), which contain photosensitive active ingredients. In particular the invention concerns TTS, which have a transparent or colorless-transparent appearance.

Various pharmaceutical effective substances, z. B. Nicotine or nifedipine, exhibits an high photosensitivity. With pharmaceutical compositions, which contain such photosensitive active ingredients, it knows bottom action Tages-bzw. Sunlight to a photochemical decomposition of the active ingredient and consequently to a significant reduction of the active substance content come, if the active substances become during the storage of the preparing up to the time of the application, or during the application duration, not protected before light admission.

With the classical application forms, like z. B. oral, parenteral or konjunctival to applizierenden dosage forms usually already, a sufficient stability becomes against influence of light thereby obtained that suitable Primär-oder becomes secondary packing selected, those the access from daylight to the active ingredient prevented. Since between the removal usually only a short period is appropriate for the preparation from the package and its administration, a decomposition of the active ingredient is to a large extent excluded due to influence of light with these medicine forms. Case a longer application duration required is, like z. B. with the application of Infusionslösun towards, the so made application usually more stationary, whereby colored or secondary-packaged Infusionsflaschen used to become to be able, in order to protect the photosensitive active ingredients against decomposition.

The measures mentioned are usually sufficient, over the stability of the too applizierenden active ingredient during the storage and/or. while the application duration too gewährlei sten.

From these classical application forms however the transdermal therapeutic systems (TTS) differ. These represent loaded systems with active ingredient, whereby the active ingredients are contained of different chemical composition in self adhesive or not-self adhesive polymers. The contained active ingredients become continuous discharged over a longer period to the skin of the patient, D. h. a TTS becomes on the skin applied and remains there for a longer period, for example some hours to several days.

Consequently the active ingredient is with the application forms mentioned (TTS) also during the application duration, dependent of the respective application place, the more or less strong daylight exposed and can during its application duration a significant, not vernachlässigba ren active substance loss experience. This can lead in the extreme case, for example with particularly photosensitive active substances, to falling below the therapeutic necessary active substance supply and endanger thus therapy success.

With on the market located TTS, which contain photosensitive active ingredients, the problem becomes usually dissolved by the fact that a aluminisierte or painted cover sheet used becomes. This forms the backing layer of the system and the covered wirkstoffhaltige matrix outward, so that the access of the daylight to wirkstoffhaltigen mA trix the minimized will and thus the active ingredient before the Zer setting becomes by sunlight protected.

For example in DE-Al-199 of 12,623 proposed TTS photosensitive to the improving the stability this will equip with colored plastic films as cover sheets.

This method of the light protection using aluminisierter, painted or colored cover sheets can be however in some cases undesirable or lead to problems or disadvantages.

The dye or Aluminisierung of highly flexible plastic films is not usually difficult and offers reliable light protection, since due to elongation of the film tears in the ink layer or in the aluminization layer can develop, which the partial entry of light into the wirkstoffhaltige polymer matrix and thus to the degradation of the active ingredient in that matrix lead can make possible.

When for colored or aluminum-coated cover sheets flexible, colored tissues offer themselves alternative, which can be occasionally high elastic. They exhibit however the disadvantage that they are of several days suitable usually not for an application, because them the environmental influences, in particular with showers, arising with it, sweating, sow-hub-look for etc., not to withstand are not able.

Aluminisierte, painted or colored cover sheets have besides the disadvantage that they are very remarkable optical and to a Stigmatisierung of the patient lead kön nen. The patient can become more recognizable with supports of TTS with such cover sheets as " di " person, which can lead to social Ausgrenzungen and on side of the patient to a Compliance or an acceptance lacking.

Object of the present invention was it therefore to make transdermal applizierbare medicine material preparing available

with a content at photosensitive active ingredients increased with which the stability is in relation to light influences, without those arise disadvantages managing specified.

According to invention will the object thereby dissolved that with transdermal therapeutic systems (TTS), whose structure wirkstoffhaltige polymer matrix and a backing layer covers and which content at at least a photosensitive active ingredient it exhibit at least, a colorless substance in the wirkstoffhaltigen matrix homogeneous distributed, absorbent in the W range, becomes, z. B. in solved or dispersed form, and/or that a such substance is in its backing layer (cover sheet) homogeneous distributed. The substance absorbent in the W-range does not have own pharmacological effect, D. h. it is not even therapeutic effective.

Photosensitive active ingredients are for example nicotine, or active ingredients from the group of the Dihydropyridinderivate, z. B. Nifedipine or Lacidipin, or Gestagene, vitamin B 12 and antibiotics, as well as salts of such photosensitive fabrics.

By the presence of an W-absorbent, colorless substance will it possible to manufacture TTS which exhibits a transparent backing layer and/or a transparent active substance matrix, and with which the protection of the photosensitive active ingredients before light-conditional decomposition ensured is nevertheless. It is particularly favourable that TTS prepared to become in this way to be able, which is perfect transparent little and is noticeable therefore during carrying on the skin. This is in particular the case if the TTS is colorless designed in accordance with an other prefered embodiment transparent and, if thus both the backing layer (cover sheet) and the polymer matrix, and if necessary other layers, transparent and colorless are.

As materials for the cover sheet of the TTS according to invention transparent films become preferably from polyester, polyethylene, polypropylene, polyurethane, ethyl vinyl acetate, polyethylene terephthalate (PET) or mixtures of such polymers used.

The wirkstoffhaltige polymer matrix of the TTS according to invention can be in or multilayer; preferably it has detention-adhesive properties. It is solid connected with the backing layer (cover sheet) and/or. a laminate forms with this. The hautseitige, detention-adhesive surface that polymer matrix becomes usually covered of a peelable protective layer or protective film, which becomes remote before the application. Also this protective film can be lichtundurchlässig victory designed.

As base materials for the polymer matrix of the TTS according to invention become prefered polyacrylates, polyisobutylenes, polydimethylsiloxanes, styrene Isopren-block copolymers or Isoprenpolymere with or without synthetic or partialsynthetischen polymers used.

In each case range becomes of a substance, also a UV absorber or an UV absorbent blockers mentioned, effected by the presence in the W that the photosensitive effect becomes material before photochemical decomposition protected.

▲ top Bottom W-range becomes the range of the electromagnetic spectrum understood, which lies between 100 Nm and 400 Nm.

For the intended purpose it is in most cases sufficient, if within the range of 250 Nm to 400 Nm absorb the W-absorbent (n) substance (EN). Prefered ones become such W-absorbent substances used, which absorb range in the W-A and/or in the UV-B-range (so called W-A-absorbers or stock absorbers).

Regarding the selection of the UV absorber will prefered that its absorptance maximum lies within that wavelength range, by which the decomposition of the used active ingredient caused becomes.

In order to reach a protection before photochemical decomposition by means of a broader W-spectral region, it is favourable, if the TTS according to invention contains a combination of at least two substances absorbent in the W-range, which exhibit different absorptance maximums.

Prefered such UV absorbers used, whose safety became already detected with the use in Kosmetikprodukten, become fundamental, or whose Anwen dung on the skin toxicological acceptable is.

The entire quantity/the added W-absorbers preferably lies within the range of 1-20 Gew. - %, particularly prefered within the range of 5-10 Gew. - %, in each case related to a TTS.

Absorbent (n) the substance (EN), in the UV range, will become/prefered from group selected, the p-aminobenzoic acid and Aminobenzoesäurederivate, preferably 4-Dimethylamino benzoesäure-2-ethyl-hexylester, 4-bis (polyethoxyl) aminobenzoesäure more polyethoxyethylester, as well as cinnamic acid and their derivatives, preferably 4-Methoxyzimtsäureisoamylester, 4Methoxyzimtsäure-2-ethylhexylester, as well as 3-Benzylidenbornan-2-on and Benzylidenbornan-2-on-Derivate, preferably 3 - (4 ') Methylbenzyliden-bornan-2-on, 3 - (4-Sulfo) benzyle idenbornan-2-on, 3 - (4 ' - trimethylammonium) benzylidenbornan2-on-Methylsulfat, as well as Salicylsäurederivate, preferably 4-Isopropylbenzylsalicylat, Salicylsäure-2-ethylhexylester, 3,3,5-Trimethyl-cyclohexyl-salicylat, as well as 2,4,6-Trianilin-p (carbo-2' ethyl hexyl i' oxy) - i, 3,5-tnazin, 3-Imidazol-4-yl-acrylsäure and their esters, 2-Phenylenbenzimidazol-5-sulfonsäure and its k, Na-und triethanolamine (=TEA) - salts, 2-Cyan-3,3-diphenyl-acrylsäure, Terephthaloyliden dicampher sulfonsaure, Butylmethoxy dibenzoyl methane, as well as benzophenones or Benzophenon derivatives, preferably Benzophenon-3, Benzophenon-4, cover.

The invention and its advantageous properties become more near explained on the basis the subsequent example.

Example: Two formulations (A, B) of a light feeling left of chen active ingredient became from the group of the Gestagene prepared, which differ in their composition by the fact that the one formulation (B) 10 Gew. - % an W-absorber contained, while the other formulation (A) did not contain W-absorber during otherwise same composition. Both detention-adhesive wirkstoffhaltigen laminates became provided with a transparent cover sheet from PET, whereby a "TTS " became obtained.

The composition of the formulation (B) is as follows: (all indications in Gew. - %) 2.0% Gestagen 87.6% acrylate polymer 0.4% crosslinker 10, 0% EusolexX 6300 Eusolex 6300 (companies Merck, Darmstadt) is a oil-soluble UV-B-absorber (3 - (4-Methylenbenzyliden) - campher).

The examination of the light protection effect both with PET film covered TTS formulations with xenon light became in accordance with the I Guideline " note for GUI thanks on the photostability testing OF new active substances and medicinal products " (CPMP/ICH/279/95) irradiated. The irradiation time amounted to 7 h, as source of irradiation became a xenon lamp used.

The used light source produced construction dependently a light output more comparable with the D65/ID65-Emissionsstandard.

Subsequent one became the active substance content into the TTS certain.

The results are in FIG. I graphic shown.

It shown itself that during the TTS formulation (B), which UV absorber contained approx. 95% of the used photosensitive active ingredient to be regained could, while during the TTS formulation (A), which did not contain W-absorber, after the irradiation only 46% of the original present active substance quantity of detected could become.

This shows that according to invention suggested the addition of W-absorbers the photochemical decomposition of active ingredients prevented and it thus possible manufacturing TTS with a content at photosensitive active ingredients as transparent TTS and improving thus their acceptance or Compliance.